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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,378	08/26/2003	Alan M. Fogelman	407T-911270US	4598

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 04/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/649,378	FOGELMAN ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) *2-26,50-122 and 187-191* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,27-38,40-49 and 123-186* is/are rejected.

7)☒ Claim(s) *39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20031114;20040601*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicant's election of the Invention of Group I, of atherosclerosis, and of SEQ ID NO:250 in the reply filed on February 28, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2-26, 50-122, and 187-191 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and sequence. Election was made **without** traverse in the reply filed on February 28, 2005.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons:

The Sequence Listing filed August 16, 2004 lists 464 sequences. However, there is an amino acid sequence at page 73, lines 9-10, of the specification which has been given the identifier "SEQ ID NO:465". This discrepancy between the number of sequences in the specification and the number of sequences in the Sequence Listing must be resolved.

If necessary, Applicant must provide a substitute computer readable form (CRF) copy of the Sequence Listing, a substitute paper copy of the Sequence Listing as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and include no new matter as required by 37 CFR 1.825(a) and (b).

The Sequence Listing filed February 9, 2004 was approved by STIC for matters of form.

3. The abstract of the disclosure is objected to because it is insufficiently detailed as to the structure of the peptides. Correction is required. See MPEP § 608.01(b).

4. The disclosure is objected to because of the following informalities: The status of the U.S. application referred to in the specification at page 34, line 16, should be updated. At page 46, line 18, "Typically" is misspelled. At page 89, line 1, the SEQ ID NO appears to be incorrect. Appropriate correction is required.

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 18, line 7, of the specification. This objection could be overcome, e.g., by deleting "http://" from the beginning of the hyperlink. Correction is required.

6. Claim 1, 27-38, 40-49, and 123-186 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear how the term "having" and the formula recited in Applicants' claim 1 should be interpreted. It is not clear if the claimed peptides are limited to peptides containing only those amino acids which are permitted by the definitions of X^1, X^2, X^3, and X^4, or if the claim terminology should be interpreted more broadly to embrace larger peptides, e.g., pentapeptides, which comprise the formula X^1-X^2-$X^3{}_n$-X^4. The more limited interpretation is believed to be consistent with Applicants' specification, e.g., at page 5, where peptides having the formula in which n=0 are described as a "trimer", and peptides having the formula in which n=1 are described as a "tetramer". However, dependent claim 38 recites that the claimed peptide can "comprise" an amino acid sequence recited in Table 4, which is

more consistent with the broader interpretation. Clarification is required. Claim 32, lines 3-4, is unclear as to whether methyl, ethyl, propyl, butyl, pentyl, and hexyl are all types of ester protecting groups, or whether "ester" is only modified by "hexyl" from the preceding list of alkyl groups. There is no antecedent basis in the claims for the phrase "said mammal" at claim 141, line 2. There is no antecedent basis in the claims for the phrase "said composition" in claim 169.

7. Claims 32, 33, 35, 46, 47, 130-174, and 181 are objected to because of the following informalities: At claim 32, lines 2 and 14, "OtBu" and "t-butoxy (tBuO)" are duplicate groups, and one of the two occurrences should be deleted. At claim 32, lines 2-3 and 11, "a benzoyl group" and "Benzoyl (Bz)" are duplicate groups, and one of the two occurrences should be deleted. At claim 32, lines 3 and 6, "carbobenzoxy" and "benzyloxycarbonyl" are duplicate groups, and one of the two occurrences should be deleted. At claim 32, line 3, a comma should be inserted after "pentyl". At claim 32, line 4, "and" should be deleted. At claim 32, lines 4-5, "a 3 to 20 carbon alkyl" is repeated, and one of the two occurrences should be deleted. The parenthetical phrase at claim 32, lines 6-7, should be deleted as being at best redundant. In the protecting group bridging claim 32, lines 15 and 16, the beginning brackets [and { at line 15 do not match the end parenthesis and bracket) and } at line 16. At claim 32, line 17, "and" should be inserted after the first comma in the line. In the protecting group at claim 32, line 17, the beginning bracket [does not match the end parenthesis). At claim 33, line 1, one of the two occurrences of "said" should be deleted. The same corrections that are made to the protecting group names recited in claim 32 should also be made to the protecting group names recited in claim 35. In claims 46 and 47, "said polypeptide" should be changed to "said peptide" so that claim language is standardized throughout the claims. At claim 130, line 2, and claim 142, line

3, "erythematosus" is misspelled. At claim 130, line 3, and claim 142, line 3, "Alzheimer's" is misspelled. At claim 130, line 3, and claim 142, line 4, either "a" should be deleted, or "illnesses" should be changed to "illness". At claim 131, line 3; claim 141, line 3; and claim 151, line 2; "one or more of" should be inserted before "the peptide" so that it is clear that not all of the peptides have to be administered simultaneously. At claim 141, line 2, the second comma after "pathology" should be deleted. At claim 152, line 3; claim 164, line 3; and claim 181, line 3; the period after "lovastatin" should be changed to a comma. At claim 162, line 4, "one or more of" should be inserted before "a peptide" so that it is clear that not all of the peptides have to be administered simultaneously. Appropriate correction is required.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

9. Claims 1, 123-128, and 131-150 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Scialdone et al (U.S. Patent Application Publication 2003/0027769). Scialdone et al teach tripeptides which inhibit angiogenesis-mediated diseases such as inflammation. Diseases to be treated include capillary proliferation in atherosclerotic plaques, and rheumatoid arthritis, and the patients to be treated include animals and humans. Specific tripeptides include Ac-Ser-Glu-Ser-NH_2 and Ac-Ser-Asp-Ser-NH_2. The tripeptides can be administered orally, in sustained release forms, and in unit dosage form, and can be administered in combination with other therapeutic compounds. Acceptable carriers include olive oil. See, e.g., the Abstract; paragraphs [0001], [0096], [0102], [0103], [0109]-[0112], and [0148]; and claims 1, 6, 14, 20, and 21.

10. Claims 129 and 130 are rejected under 35 U.S.C. 103(a) as being obvious over Scialdone et al (U.S. Patent Application Publication 2003/0027769). Application of Scialdone et al is the same as in the above rejection of claims 1, 123-128, and 131-150. Scialdone et al do not teach their tripeptides in kit form including instructional materials for use. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to manufacture the tripeptides of Scialdone et al in kit form including instructional materials because it is well-known in the pharmaceutical arts to produce therapeutic agents in kit form including instructional materials for use because of the ease of storage, transportation, measurement, and administration.

11. Claims 151-178 and 181-185 are rejected under 35 U.S.C. 103(a) as being obvious over Scialdone et al (U.S. Patent Application Publication 2003/0027769) as applied against claims 1, 123-128, and 131-150 above, and further in view of the WO Patent Application 97/36927. Scialdone et al teach using their tripeptides to treat angiogenic symptoms of atherosclerosis, and teach that their tripeptides can be combined with other therapeutic agents, but do not teach combining their tripeptides with statins. The WO Patent Application '927 teaches the co-administration of statins such lovastatin and simvastatin with peptide therapeutic agents in order to prevent or treat atherosclerosis. See, e.g., the Abstract; page 20, line 12 - page 21, line 8; and claims 43-50. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the tripeptides of Scialdone et al with the statins of the WO Patent Application '927 in order to treat atherosclerosis because the tripeptides and statins are used to treat the same disease, because both Scialdone et al and the WO Patent Application '927 teach that their active agents can usefully be combined with other active agents,

and because it is prima facie obvious to use a combination of two materials each of which has been used separately for the same process. In re Kerkhoven, 205 USPQ 1069, 1072 (CAFC 1980).

12. Claims 133 and 186 are rejected under 35 U.S.C. 103(a) as being obvious over Scialdone et al (U.S. Patent Application Publication 2003/0027769) in view of the WO Patent Application 97/36927 as applied against claims 151-178 and 181-185 above, and further in view of Fogelman et al (U.S. Patent Application Publication 2003/0040505) or Bertelli (U.S. Patent No. 4,684,520). Scialdone et al and the WO Patent Application '927 do not teach co-formulation of a phospholipid with their tripeptides or statins. Fogelman et al teach that phospholipids can be administered in order to ameliorate symptoms of atherosclerosis in an animal. See, e.g., claims 1-81. Bertelli et al teach that phospholipids can be administered in order to treat atherosclerosis. See, e.g., the Abstract; column 5, line 58 - column 6, line 3; and claims 1-4. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use a combination of the tripeptides of Scialdone et al, the statins of the WO Patent Application '927, and the phospholipids of Fogelman et al or Bertelli to treat atherosclerosis in a mammal, because the tripeptides of Scialdone et al, the statins of the WO Patent Application '927, and the phospholipids of Fogelman et al and Bertelli are used for the same purpose, because the use of multiple drugs to treat the same disease or condition is routine in the pharmaceutical arts and in the atherosclerosis treatment arts as shown by Scialdone et al and the WO Patent Application '927, and because it is prima facie obvious to use a combination of two materials each of which has been used separately for the same process. In re Kerkhoven, 205 USPQ 1069, 1072 (CAFC 1980).

13. Claims 175, 179, 180, and 182 are rejected under 35 U.S.C. 103(a) as being obvious over Scialdone et al (U.S. Patent Application Publication 2003/0027769) as applied against claims 1, 123-128, and 131-150 above, and further in view of Acton et al (U.S. Patent Application Publication 2002/0042441). Scialdone et al teach using their tripeptides to treat angiogenic symptoms of atherosclerosis, and teach that their tripeptides can be combined with other therapeutic agents, but do not teach combining their tripeptides with ezetimibe. Acton et al teach the co-administration of ezetimibe with other therapeutic agents in order to prevent or treat atherosclerosis. See, e.g., the Abstract and paragraph [0127]. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the tripeptides of Scialdone et al with the ezetimibe of Acton et al in order to treat atherosclerosis because the tripeptides and ezetimibe are used to treat the same disease, because both Scialdone et al and Acton et al teach that their active agents can usefully be combined with other active agents, and because it is prima facie obvious to use a combination of two materials each of which has been used separately for the same process. In re Kerkhoven, 205 USPQ 1069, 1072 (CAFC 1980).

14. Claims 1, 27-29, 31, 32, 43-48, and 123-128 are rejected under 35 U.S.C. 102(b) as being anticipated by Bogden (U.S. Patent No. 5,595,973). Bogden teaches the tetrapeptide N-Acetyl-Ser-Asp-Lys-Pro, which is used therapeutically to promote regeneration of hemopoietic cells. the tetrapeptide can be administered orally or by intravenous injection, can be administered by a subcutaneous infusion pump, and can be in unit formulation. See, e.g., column 3, lines 3-27, and claims 1 and 2. In view of the identity in structure between Bogden's tetrapeptide and Applicants' claimed tetrapeptide, Bogden's tetrapeptide inherently will ameliorate one or more symptoms of an inflammatory condition, inherently will convert pro-inflammatory HDL to anti-

inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory, inherently will protect a phospholipid against oxidation by an oxidizing agent to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the tetrapeptide of Bogden and Applicants' claimed tetrapeptides to shift the burden to Applicants to provide evidence that the claimed tetrapeptides are unobviously different than the tetrapeptide of Bogden.

15. Claims 129 and 130 are rejected under 35 U.S.C. 103(a) as being obvious over Bogden (U.S. Patent No. 5,595,973). Application of Bogden is the same as in the above rejection of claims 1, 123-128, and 131-150. Bogden does not teach their tripeptides in kit form including instructional materials for use. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to manufacture the tripeptides of Bogden in kit form including instructional materials because it is well-known in the pharmaceutical arts to produce therapeutic agents in kit form including instructional materials for use because of the ease of storage, transportation, measurement, and administration. Applicants' claimed content of instructions in the kit claims does not impart patentability to the kit claims. Compare In re Ngai, 70 USPQ2d 1862 (CAFC 2004).

16. Claims 1, 27-29, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Heavner et al (U.S. Patent No. 5,298,490). Heavner et al teach the inactive peptide Ala-Lys-Asp-Val. See, e.g., Figure 1 and column 16, lines 2-3. Note that a prior art compound need not have a patentable utility in order to anticipate claims drawn to the same compound. See MPEP 2122. In view of the identity in structure between Heavner et al's tetrapeptide and Applicants' claimed tetrapeptide, Heavner et al's tetrapeptide inherently will ameliorate one or more

symptoms of an inflammatory condition, inherently will convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory, inherently will protect a phospholipid against oxidation by an oxidizing agent to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the tetrapeptide of Heavner et al and Applicants' claimed tetrapeptides to shift the burden to Applicants to provide evidence that the claimed tetrapeptides are unobviously different than the tetrapeptide of Heavner et al.

17. Claims 1, 27, 40, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 96/41815. The WO Patent Application '815 teaches tetrapeptides designated 4, 8, and 12, at pages 3-4 of the specification. In view of the identity in structure between the WO Patent Application '815's tetrapeptides and Applicants' claimed tetrapeptides, the WO Patent Application '815's tetrapeptides inherently will ameliorate one or more symptoms of an inflammatory condition, inherently will convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory, inherently will protect a phospholipid against oxidation by an oxidizing agent to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the tetrapeptides of the WO Patent Application '815 and Applicants' claimed tetrapeptides to shift the burden to Applicants to provide evidence that the claimed tetrapeptides are unobviously different than the tetrapeptides of the WO Patent Application '815.

A translation of the WO Patent Application '815 has been ordered. If after receipt of the translation, additional rejections of the claims are appropriate, the examiner will make them in the next Office action.

18. Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by the Tan et al article (J. Immun. Meth., Vol. 205, pages 201-209). The Tan et al article teaches the peptide KLVDFRELNK (see Table 3, first entry), which comprises the amino acid sequence Phe-Arg-Glu-Leu of SEQ ID NO :250 from Applicants' Table 4. This rejection assumes that the claim language "comprises" permits amino acids to be present in the peptide in addition to those which are present in the amino acid sequence of a peptide in Table 4. See also the above rejection under 35 U.S.C. 112, second paragraph. In view of the similarity in structure between the Tan et al article's peptide and Applicants' claimed peptide, the Tan et al article's peptide inherently will ameliorate one or more symptoms of an inflammatory condition, inherently will convert pro-inflammatory HDL to anti-inflammatory HDL or make anti-inflammatory HDL more anti-inflammatory, inherently will protect a phospholipid against oxidation by an oxidizing agent to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed to be present between the peptide of the Tan et al article and Applicants' claimed peptides to shift the burden to Applicants to provide evidence that the claimed tetrapeptides are unobviously different than the tetrapeptide of the Tan et al article.

19. Claims 1, 123-128, and 131-150 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Haviv et al (U.S. Patent Application Publication 2003/0125260). Haviv et al teach tetrapeptides which inhibit angiogenesis-mediated diseases such as inflammation. Diseases to be treated include capillary proliferation in atherosclerotic plaques and rheumatoid arthritis, and the patients to be treated include humans and other mammals. Specific tetrapeptides are N- and C-terminally protected, and include D-amino acids. The tetrapeptides can be administered rectally, intraperitoneally, intravascularly, subcutaneously, transcutaneously,

intramuscularly, and by inhalation, in sustained release forms (which also constitute unit dosage forms), and in aqueous solution form, and can be administered in combination with other therapeutic compounds. Acceptable carriers include olive oil. See, e.g., the Abstract; paragraphs [0035]-[0040] and [0050]; and claims 4, 6, 8, and 10. Note that the aqueous solution forms of the tetrapeptides are capable of being administered orally. An intended use limitation does not impart patentability to product claims where the product is otherwise anticipated by or obvious over the prior art.

20. Claims 129 and 130 are rejected under 35 U.S.C. 103(a) as being obvious over Haviv et al (U.S. Patent Application Publication 2003/0125260). Application of Haviv et al is the same as in the above rejection of claims 1, 123-128, and 131-150. Haviv et al do not teach their tetrapeptides in kit form including instructional materials for use. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to manufacture the tetrapeptides of Haviv et al in kit form including instructional materials because it is well-known in the pharmaceutical arts to produce therapeutic agents in kit form including instructional materials for use because of the ease of storage, transportation, measurement, and administration.

21. Claims 151-178 and 181-185 are rejected under 35 U.S.C. 103(a) as being obvious over Haviv et al (U.S. Patent Application Publication 2003/0125260) as applied against claims 1, 123-128, and 131-150 above, and further in view of the WO Patent Application 97/36927. Haviv et al teach using their tetrapeptides to treat angiogenic symptoms of atherosclerosis, and teach that their tetrapeptides can be combined with other therapeutic agents, but do not teach combining their tetrapeptides with statins. The WO Patent Application '927 teaches the co-administration of statins such lovastatin and simvastatin with peptide therapeutic agents in order to prevent or

treat atherosclerosis. See, e.g., the Abstract; page 20, line 12 - page 21, line 8; and claims 43-50. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the tetrapeptides of Haviv et al with the statins of the WO Patent Application '927 in order to treat atherosclerosis because the tetrapeptides and statins are used to treat the same disease, because both Haviv et al and the WO Patent Application '927 teach that their active agents can usefully be combined with other active agents, and because it is prima facie obvious to use a combination of two materials each of which has been used separately for the same process. In re Kerkhoven, 205 USPQ 1069, 1072 (CAFC 1980).

22. Claims 133 and 186 are rejected under 35 U.S.C. 103(a) as being obvious over Haviv et al (U.S. Patent Application Publication 2003/0125260) in view of the WO Patent Application 97/36927 as applied against claims 151-178 and 181-185 above, and further in view of Fogelman et al (U.S. Patent Application Publication 2003/0040505) or Bertelli (U.S. Patent No. 4,684,520). Haviv et al and the WO Patent Application '927 do not teach co-formulation of a phospholipid with their tetrapeptides or statins. Fogelman et al teach that phospholipids can be administered in order to ameliorate symptoms of atherosclerosis in an animal. See, e.g., claims 1-81. Bertelli et al teach that phospholipids can be administered in order to treat atherosclerosis. See, e.g., the Abstract; column 5, line 58 - column 6, line 3; and claims 1-4. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use a combination of the tetrapeptides of Haviv et al, the statins of the WO Patent Application '927, and the phospholipids of Fogelman et al or Bertelli to treat atherosclerosis in a mammal, because the tetrapeptides of Haviv et al, the statins of the WO Patent Application '927, and the phospholipids of Fogelman et al and Bertelli are used for the same purpose, because the use of multiple drugs

to treat the same disease or condition is routine in the pharmaceutical arts and in the atherosclerosis treatment arts as shown by Haviv et al and the WO Patent Application '927, and because it is prima facie obvious to use a combination of two materials each of which has been used separately for the same process. In re Kerkhoven, 205 USPQ 1069, 1072 (CAFC 1980).

23. Claims 175, 179, 180, and 182 are rejected under 35 U.S.C. 103(a) as being obvious over Haviv et al (U.S. Patent Application Publication 2003/0125260) as applied against claims 1, 123-128, and 131-150 above, and further in view of Acton et al (U.S. Patent Application Publication 2002/0042441). Haviv et al teach using their tetrapeptides to treat angiogenic symptoms of atherosclerosis, and teach that their tetrapeptides can be combined with other therapeutic agents, but do not teach combining their tetrapeptides with ezetimibe. Acton et al teach the co-administration of ezetimibe with other therapeutic agents in order to prevent or treat atherosclerosis. See, e.g., the Abstract and paragraph [0127]. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the tetrapeptides of Haviv et al with the ezetimibe of Acton et al in order to treat atherosclerosis because the tetrapeptides and ezetimibe are used to treat the same disease, because both Haviv et al and Acton et al teach that their active agents can usefully be combined with other active agents, and because it is prima facie obvious to use a combination of two materials each of which has been used separately for the same process. In re Kerkhoven, 205 USPQ 1069, 1072 (CAFC 1980).

24. Claims 30, 33-37, 41, 42, and 49 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, and the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The

prior art of record does not teach or suggest compounds having these structures. Composition claims comprising these tetrapeptides, and method claims using these tetrapeptides, would also be novel and unobvious over the prior art of record or any combination thereof.

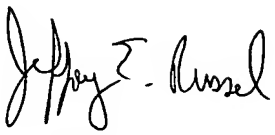
Claim 49 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and if re-written so as to be limited to the elected sequence SEQ ID NO:250, plus the sequence SEQ ID NO:337, both of which have the amino acid sequence Phe-Arg-Glu-Leu. These compounds are novel and unobvious over the prior art of record or any combination thereof, which does not teach or suggest tetrapeptides having the recited structures. Composition claims comprising these tetrapeptides, and method claims using these tetrapeptides, would also be novel and unobvious over the prior art of record or any combination thereof.

25. In the Information Disclosure Statement filed June 1, 2004, the bottom of the listing of references states "Page 1 of 2"; however, the examiner has not been able to locate a second page of the listing of references. Applicants are requested to check as to whether there is a second page of listed references, and if so to re-submit the second page.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications

such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

April 15, 2005